REMARKS

Claims 35 and 36 are pending in the application. Claim 35 has been withdrawn as being directed to a non-elected invention. No new matter is added.

The Office Action contains a single rejection of claim 36 under 35 U.S.C. § 102(b) as being anticipated by Forssmann et al. (EP 0349545) as evidenced by Nutt et al. (U.S. Patent No. 5,057,603). This rejection is traversed.

Forssmann et al. show a polypeptide having an amino acid sequence similar to that of present claim 36 part (b), except that the H at the start of the sequence and the Acm with the first Cys are absent from the Forssmann et al. sequence. However, the Examiner asserts that the treatment steps in Example 3 of Forssmann et al. would result in a mixture that contained some fragments having the sequence of present claim 35 part (b) for a short period of time.

The present inventors have synthesized a purified protected polypeptide [ANP (95-126); Claim 36(a); SEQ ID 10] from purified protected polypeptide fragments of present claim 35(a) to (g) (SEQ ID 6 to 9). During all chemical steps of the coupling of the fragments corresponding to SEQ ID 6 to 9 to obtain the polypeptide of Claim 36(a) the cysteine residue at amino acid position 11 is protected by acetamidomethyl (Acm). The cysteine residue at amino acid residue position 1 of SEQ ID 8 (Claim 35(c) to (e) is protected by the trityl group during chemical synthesis resulting in the polypeptide of Claim 36(a) (SEQ ID 10). Treatment of the protected polypeptide of Claim 36(a) by trifluroacetic acid yields exclusively the polypeptide according to Claim 36(b) (SEQ ID 5) with an Acm-group at the cysteine residue of position 11, and with no protective group at the cysteine of position 27.

Forssmann et al. teach the synthesis of a polypeptide using a stepwise solid-phase synthesis approach. They used Acm-protection for both cysteine residues present in the targeted polypeptide. Cleavage by hydrogen fluoride results in a polypeptide with two Acm-protected cysteine residues. The two present Acm-groups are then cleaved within 15 minutes by treatment with a high excess of iodine yielding directly the disulfide-bonded ANP (95-126).

Acm-groups exhibit an identical reactivity when exposed to iodine. They react with identical kinetics. Under the used conditions of the iodine treatment in Forssmann et al., in particular the significant excess of 10 equivalents of iodine and the very short reaction time of 15 minutes, no selectivity of Acm-cleavge can be achieved. That such selectivity cannot be achieved in general is reflected by the fact that Acm-protection is almost exclusively used to connect two correspondingly protected cysteine residues by a disulfide bond. There is a large body of scientific reports demonstrating the synthesis of disulfide-containing peptides from precursors with two Acm-groups, e.g. (i) Moroder et al., Oxidative Folding of Cystine-rich Peptides vs Regioselective Cysteine Pairing Strategies, Biopolymers (Peptide Science), 40, 1996, 207; (ii) Büllesbach, Site-directed Disulfide Formation in Peptide Synthesis, Kontakte (Darmstadt), 1, 1992, 21; (iii) Kamber, The Synthesis of Cysteine Peptides by Iodine Oxidation of S-Trityl-cysteine and S-Acetamidomethy-cysteine Peptides, Helvetica Chimica Acta, 63, 1980, 899, and references cited therein. None of those publications reports the synthesis, even an intermediate, of a polypeptide with one Acm-group from a precursor which contains two Acm-groups.

Furthermore, the material described in Example 3 by Forssmann et al. corresponds to a non-purified material. All chemical steps are carried out without any purification or enrichment of the targeted polypeptide.

The present inventors have described all synthesis of ANP (95-126) from protected polypeptide fragments in solution. All fragments are subjected to extractive procedures resulting in highly purified fragments. The corresponding purified fragments are then used to assemble the target polypeptide according to claim 36(a) (SEQ ID 10). As not only the three fragments are purified, but also the intermediates before obtaining the complete polypeptide corresponding to SEQ ID 10, the entire synthetic process involves purification steps. Forssmann et al. describe a purification only after the iodine treatment, i.e. the last chemical step.

For at least the above reasons, reconsideration and withdrawal of the rejection of claim 36 under 35 U.S.C. § 102(b) are respectfully requested.

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, making reference to Attorney Docket No. 108099-00001.

Respectfully submitted,

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